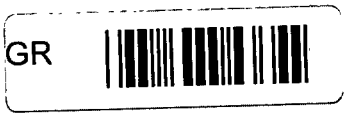

ORIGINAL SUBMISSION

BioNeutra Inc.

Transforming Natural Products into Better Health

#132, Advanced Technology Center
Edmonton Research Park
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Alberta T6N 1G1, CANADA
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06 June, 2005

Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food And Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835
USA

Dear Sir or Madam:

Please find enclosed a GRAS exemption claim for our product Isomalto-oligosaccharide (IMO) along with the all-relevant required information.

This short-chain carbohydrate is enzymatically transformed from starch, and starch is processed from the cereal crops, like wheat, barely, potato etc.

IMO is being used as a general sweetener in a variety of food and beverage products. Having properties of prebiotic and low calorie, scientific studies suggested a number of health benefits with minimal chance of an adverse reaction or harmful effects.

We cited all the available scientific data as well as market information for the safe consumption of IMO. Based upon our current knowledge about the consumption of IMO, we determined that use of this sweetener is GRAS and it is exempt from the pre-market approval requirements of FDA.

Please contact with us, if any further information is required in this respect.

Yours truly,

Jianhua Zhu, Ph. D.
President/CEO
BioNeutra Inc.

Encl: GRAS Notice

GRAS Notice

(GRAS exemption claim for Isomalto-oligosaccharide or IMO)

i. Name & Address:

BioNeutra Inc.
#132, Advanced Technology Center
Edmonton Research Park
9650-20 Ave., Edmonton, Alberta T6N 1G1, Canada
Tel: (780) 466-1481
Fax: (780) 46601491
Email: office @bioneutra.ca

ii. Common Name of the Product:

Isomalto-oligosaccharide (IMO)

iii. Applicable conditions of use:

Isomalto-oligosaccharide (IMO) is a non-digestible, low calorie health sweetener that supports the proliferation of the beneficial bacteria residing in the large intestine (colon), therefore act as a Prebiotic. The general population uses IMO as a low-calorie sweetener mixing with a variety of other foods and beverages products for the purpose of sweetening. This product will be supplied to the followings major food industries to be used as a low-calorie, bulk sweetener and as a general food ingredient;

a) Beverage Industries
b) Dairy Industries
c) All kinds of sweets and dessert's making industries

IMO will also be used by other related industries, e.g., nutrition bars, tofu, fish paste, biscuits, cakes, confectionery, Candy and chocolate bars, milk products, instant powders, powder milk, yogurts, ice-creams, sorbets, sherbets, jams, jellies, muffins, cereals, soups and home cooking ingredients.

IMO is mildly sweet and can be used to replace maltose syrup. IMO can reproduce bifidobacterium by 2 to 4 times. IMO's sweetness is about 60-70% that of sugar (sucrose) and it is easily utilized by intestinal bacteria. Since it is only slightly degradable by glucoamylase, this compound is used as a light sweetener for sweet sake and sake. Japanese companies are leading the world in the research, development and production of

oligosaccharides. In Japan, the use of IMO is more prevalent than another oligosaccharide.

As IMO does not influence blood sugar or insulin levels and it does not absorbed in the small intestine, therefore, is consumed by the diabetic populations as well. IMO improves overall gastrointestinal and bowl functions in human in addition to having low calories.
It has been reported in clinical trials that IMO do not cause any GI upset when consumed up to 10-20 g/day. Generally, IMO has been reported to be safe up to 30g/day per adult individual.

iv. Scientific basis for the GRAS determination:

Oligosaccharides are major compounds found in various products and recently, their use in functional foods has increased and further researched. Some classes of oligosaccharides are non-digestible in the upper gastrointestinal tract and thus considered as a prebiotics. Prebiotic is defined as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, that can improve the host health" (Gibson 1995, chow 2002). Of the natural non-digestible oligosachharides that fulfill the criteria of a colonic food, Isomalto-oligosaccharide (IMO) is meeting all criteria allowing classification as prebiotics.

IMO is found to be effective at increasing the numbers of bifidobacteria and lactate and improve the intestinal microflora in general, therefore, is safe to categorize as a Prebiotic (Rycroft 2001, Komoto 1988).

Currently, there are at least three prebiotics used in Europe and USA. These are fructans (Inulin and fructo-oligosaccharides) and galagcto-oligosaccharides. The range of oligosacchariedes sold in the Japanese market is more extensive and clinical evaluations are underway for the new emerging oligosachardes. IMO are added to a number of functional foods sold in Japan that claimed to have health benefits, as a result of the prebiotic function of the IMO. IMO is one of the new emerging oligosaccharide with its characteristics of prebiotics. Although, there is still insufficient data about its fermentation properties but according to the studies performed till now, it is quite evident that this molecule might have the similar or more desirable properties than the established ones, like FOS & GOS.

Besides the health related functions, IMO's possible toxic effects were evaluated and appeared recently in scientific literature (Donal 2003). Results showed that IMO-supplemented food is completely non-toxic. A diet with 5-20% IMO was also shown to reduce the abdominal fat tissue in

mammals. Under the same title, the effect of IMO-supplemented food on blood glucose level was predicted and expected to be effective therapeutically for diabetes or pre-diabetes.

Generally, there is no any report that showed any sever side effects or adverse reactions with IMO consumption by healthy individuals. IMO is effective at increasing numbers of bifidobacterium and lactate whilst generating the least gas (Rycroft 2001). The consumption of IMO up to 15 g per day did not made any effect on the blood lipid concentration and glucose absorption among young healthy adults (van Dokkum 1999). The maximum permissible dose of IMO that does not cause diarrhea is estimated >1.5 g/kg body wt. (i.e., about 15-20 g/day), which is higher then any given sugar substitutes (Oku 2002). This represents the least health related risk associated with this type of oligosaccharide.

The use and safety of IMO was also evaluated in the patients with hemodialysis suffering chronic constipation and hyperlipidimea. IMO treatment was well tolerated and effective in increasing bowel frequency and improving constipation in hyperlipidimea patient (Wang 2001). In addition, IMO treatment was effective in lowering total cholesterol and triglycerides. There was no side effect or adverse effect of IMO consumption was reported among hemodoalysis patients.

With the high dose of IMO then recommended, there is possibility of gastrointestinal symptoms (like production of copious amounts of gas, bloating, soft stool or diarrhea) with the dose that is about 40 times higher than the no-effect level for laxative effects in humans. Therefore, consumption of IMO within the recommended dosage is not expecting to pose any health-related concern.

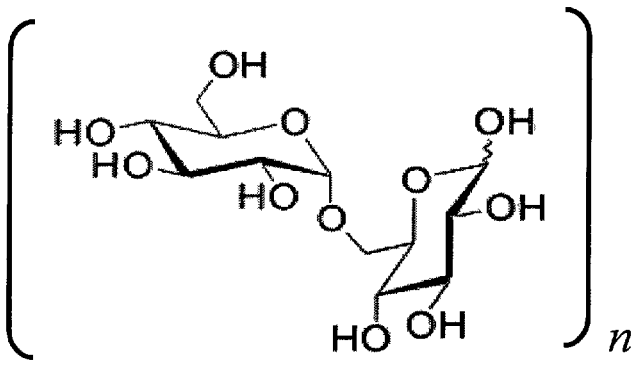
(2) Identity of the Product

COMPOSITION OF THE PRODUCT

IMO is a branched oligosaccharide containing a series of α-(1,6) bonds in its structure. It is made by liquescent starch being treated with the enzymes; β-amylase, pullulanase, and transglucosidase. IMO is produced by the enzymatic transformation of starch (starch is processed from cereal crops like wheat, barely or potatoes). IMO is a mixture of glucose oligomers such as isomaltose, panose, isomaltotriose, isomaltotetrose, isomaltopentose, isomaltoshexose and isomaltoheptose (Frost and Sullivan, 2003).

Isomaltose (6-*O*-α-D-glucopyranosyl-D-glucose) is formed from two glucose monosaccharides. It is often found at the branching points of amylopectin and glycogen. IMO is the repeating of the 6-*O*-α-D-glucopyranosyl-D-glucose up to 4-7 units.

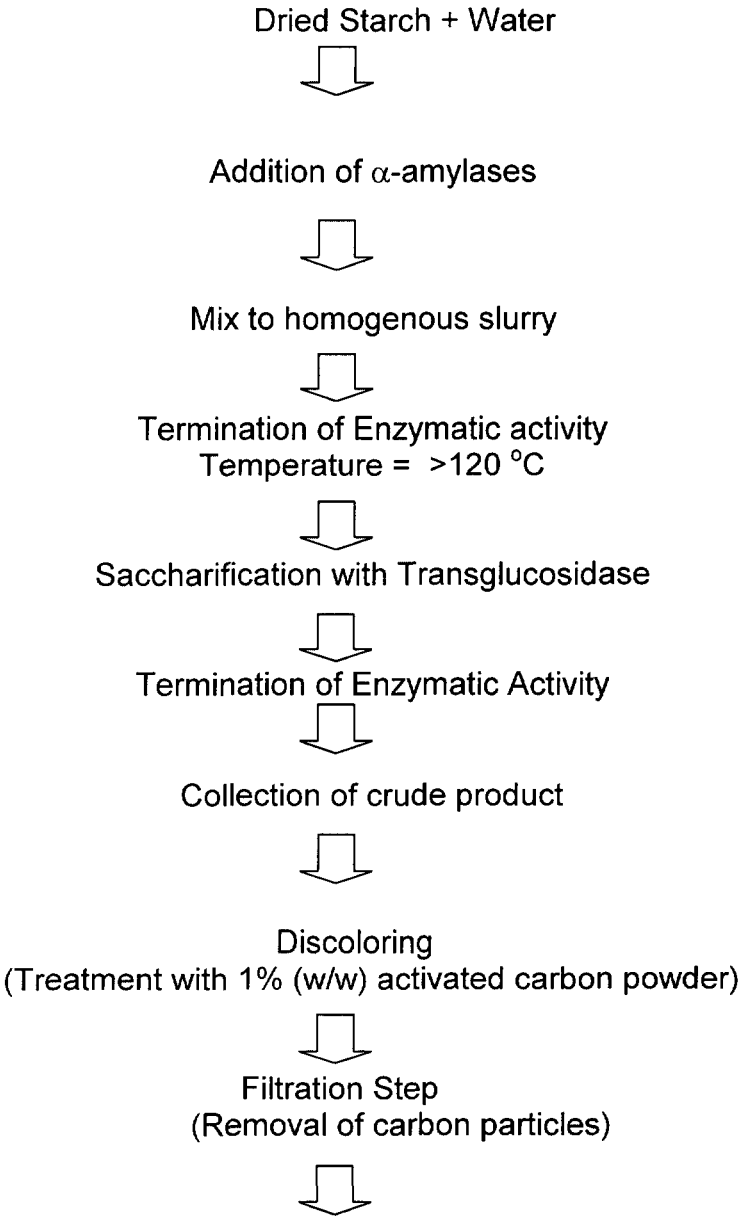
The structural formula of isomaltose is represented below;



Process steps involved in Manufacturing of IMO (Isomalto-oligosaccharide)

- Isomalto-oligosaccharide (IMO) is enzymatically transformed from Starch, and starch is obtained either from wheat, barely or potato.
- Starch is used as a starting raw material

Following is the summarized flow diagram of the process involved in manufacturing of IMO;



000007

Sequential Ion-exchange Columns system
(Removal of protein & salt contaminants)

⇩

Concentration Step

⇩

Final Product (Isomalto-oligosaccharide)
QC Testing of the Final Products
(Sugar content analysis, Microbial contamination level)

Product Information:

Any animal tissues used in the processing of this product:	None
Medicinal Ingredients used:	None
Non-medicinal Ingredients:	Isomalto-oligosaccharide
Standard or Grad:	As per BioNeutra Standard (see below)*
Common Name:	Isomalto-oligosaccharide
Amount & Recommended dosage:	
(if taken in form of pills or capsules)	2.5-5.0 g/dose
(if taken as bulk sweetener mixed with other foods and beverages)	30 g/ day (Adult)
Purpose:	A low calorie health sweetener and a prebiotic
Source:	Starch from Wheat, Barely or Potato
Recommended use or Purpose:	Low calorie health sweetener and a prebiotic to improve over all bowel functions
Dosage Form:	Powder or Syrup
Duration of Use:	As long as there is no any gastrointestinal discomfort or adverse effects

000008

Sterile:	No
Rout of Administration:	Orally
Sub-population group:	Healthy Adults, Diabetic patients, Children
Risk Information:	None Reported
Cautions and Warnings:	Cautions: In case of gastrointestinal discomfort or abdominal bloating, IMO use should be discontinued Warnings: Very high dosages (> 40 g/day) may develop gastro-intestinal discomfort
Contra-Indications:	None reported
Known Adverse Reactions:	None reported

Product Specifications:

(a) *Specification for Isomalto-oligosaccharide (IMO-900) (Syrup)

ITEMS	INDEX
Appearance:	Transparent sticky syrup with pale yellow color or Colorless, with no visible particulates, light sweet in taste
Dried Solids (g/100g)	≥ 75
pH	4.0 ~ 6.0
Glucose (% based on dried solids)	≤ 5
Isomaltose+ Panose + Maltose(G_3) % based on dried solids)	≥ 45
Total Non- Fermentable IMO (% based on dried solids)	≥ 90
Sulfated Ash (g/100 ml)	≤ 0.3
Arsenic (mg/kg)	≤ 0.5
Lead (mg/kg)	≤ 0.5
Total Aerobic Count (CFU/g)	$< 1 \times 10^4$
Yeast & Mold (CFU/g)	$< 1 \times 10^2$
E. Coli (MPN/g)	$< 1 \times 10^1$
Salmonella (CFU/g)	Absent
Pathogenic bacteria (CFU/g)	Absent

000010

(b) *Specification for Isomalto-oligosaccharide (IMO-900) (Powder)

ITEMS		INDEX
Physical Appearance:	White powder with no any contaminating particles Light-sweet in taste	
Moisture (%)		≤ 4
Solubility (%)		≥ 99
pH		4.0 ~ 6.0
Glucose (% based on dried solids)		≤ 5
Isomaltose+ Panose + Maltose(G_3) (% based on dried solids)		≥ 45
Total Non- Fermentable IMO (% based on dried solids)		≥ 90
Sulfated Ash (g/100g)		≤ 0.3
Arsenic (mg/kg)		≤ 0.5
Led (mg/kg)		≤ 0.5
Total aerobic count (CFU/g)		$< 1 \times 10^4$
Yeast (CFU/g)		$< 1 \times 10^2$
E. Coli (MPN/g)		$< 1 \times 10^1$
Salmonella (CFU/g)		Absent
Pathogenic bacteria (CFU/g)		Absent

(3) Self-limiting levels of product use:

IMO can be marketed under two categories – as a general sweetener or as a prebiotic. As a low-calorie general sweetener, IMO will be sold to intermediate markets for food processors, dairy producers, confectionaries producers, beverage producers and nutritional supplement manufacturers. As a functional food ingredient and a Nutraceutical (prebiotic), IMO will be sold directly to the public.

Use of IMO as a general sweetener:	Maximum 30 g/ day (Up to 25 per cent of total content in any given food item)

Use of IMO as a Functional health ingredient:

If taken in form of pills or capsules	2.5-5.0 g/dose

Adults: 1 to 2 teaspoon, 3 times daily (Syrup or Powder form)
Children: 1/2 to 1 teaspoon, 3 times daily

(1 teaspoon = about 5 ml syrup or 2.5 gram powder)

Amount exceeding 40 g/day may cause GI upset, like copious amount of gas, bloating and soft stool/mild diarrhea

(4) Summary for the basis of GRAS:

Oligosaccharides are major compounds found in various products and recently, their use in functional foods has increased and further investigated. Some classes of oligosaccharides are non-digestible in the upper gastrointestinal tract and thus considered as a prebiotics. IMO is found to be effective at increasing the numbers of bifidobacteria and lactate and improve the intestinal microflora in general, therefore, is safe to categorize as a Prebiotic (Rycroft 2001, Komoto 1988).

According to the IFIC (International Food Information Council, Washington, D.C.), 95% of those surveyed agreed with the statement that short chain oligosaccharides provide health benefits for disease prevention. This is further supported by the fact that there is strong link between the use of fiber and reduced risk of colon cancer as well as beneficial effect of calcium on osteoporosis (Tahiri 2003, Buecher 2003). In addition, IMO increases the production of beneficial short-chain fatty acids such as butyrate and the absorption of calcium and magnesium (Kashimura 1996).

Currently, there are at least three prebiotics used in Europe and USA. These are fructans (Inulin & fructo-oligosaccharides) and galagcto-oligosaccharides. The range of oligosacchariedes sold in the Japanese market is more extensive and clinical evaluations are underway for the new emerging oligosachardes. IMO are added to a number of functional foods sold in Japan that claimed to have health benefits, as a result of the prebiotic function of the IMO. Although, there is still insufficient data about its fermentation properties but according to the studies performed till now, it is quite evident that this molecule might have the same or more desirable properties than the established ones, like Fructo-oligosaccharide (FOS). FOS has already been granted a GRAS status by FDA (GRAS Notice No. GRN 000044).

Besides the health related functions, IMO's possible toxic effects were evaluated and appeared recently in scientific literature (Donal 2003). Results showed that IMO-supplemented food is completely non-toxic. A diet with 5-20% IMO was also shown to reduce the abdominal fat tissue in mammals. Under the same title, the effect of IMO-supplemented food on blood glucose level was predicted and expected to be effective therapeutically for diabetes or pre-diabetes. The safety of IMO was also evaluated in the patients with hemodialysis suffering chronic constipation and hyperlipidimea. There was no side effect or adverse effect of IMO consumption was reported among hemodoalysis patients.

In Canada, IMO is categorized under general food ingredients by Canadian Food Inspection Agency (CFIA) and by Regional Food Program, and are allowed to sell in the Canadian market. Health Canada allowed these products to be sold in Canadian market as a bulk sweetener & a food ingredient.

In Europe, "Scientific Committee's Report on Food for Human Consumption" has authorized the sale of these oligosaccharides in European market. *(43rd series, 2000).*

In Japan, China, Hong Kong, Korea and Taiwan, regulatory approval for the sale of these oligosaccharides has already been given and these products are in market for many years.

Listing of Scientific Evidence

* Randomized Control Trial (Reference in bold are available in hard copy)

Type and Level of Evidence	Dosage: Dose, Dosage form, Frequency and route of administration	Duration, If any	Risk Information a) Caution or Warning b) Contraindication c) Adverse Reaction d) Other	Human: Animal; or *In vitro*	Design, Results and Conclusions	References
RCT* Level 1	10g/d, oral	30 days	a) None reported b) None reported c) None reported d) None reported	Human Adults	**Design:** Seven older male subjects administered a 30-day IMO (10g) supplement. Bowel function were monitored daily. Fecal characterstics and other parameters noted. **Results:** Incorporation of IMO in food supplement significantly increased the defecation frequency, wet stool output and dry stool weight. Organic acids also increased in stool. **Conclusion:** Consumption of IMO effectively improved bowel movement, stool output and microbial fermentation in the colon without any adverse effect.	**Chen et at., 2001**

Trial Type and Level of Evidence	**Dosage: Dose, Dosage form, Frequency and route of administration**	**Duration, If any**	**Risk Information** a) Caution or Warning b) Contraindication c) Adverse Reaction d) Other	**Human: Animal; or *In vitro***	**Design, Results and Conclusions**	**References**
RCT* Level 1	3-10% of IMO-H to total diet/d (15.3 –43.4 g/kg of b.w, orally administered	16 weeks	a) None reported b) None reported c) None reported d) None reported	Human and Animal	**Design:** (a) Male Rats were fed a diet containing 3-10% IMO-H for 16 weeks. (b) At a single dose level of 15.3, 21.7, 30.7 or 43.4 g/kg of IMO-H was orally administered to rats. (c) A mutagenecity test and chromosome tests performed for genotoxic potential. (d) 20 healthy men given IMO-H and Maltitol. **Results & Conclusions:** (a) No dose-related and toxic change of IMO-H feeding was observed in rats (b) Mortality increased as the dose increased with LD50 estimated 32.4 g/kg. (c) No indications of genetoxic potential. (d) IMO-H is a less toxic sugar substitute and the laxative effect in human is lower than that of general sugar alcohols.	**Tsunehiro et al., 1998)**

Type and Level of Evidence	Dosage: Dose, Dosage form, Frequency and route of administration	Duration, If any	Risk Information a) Caution or Warning b) Contraindication c) Adverse Reactior d) Other	Human: Animal; or *In vitro*	Design, Results and Conclusions	References
RCT* Level 1	15 g/d, orally	7 days	a) None reported b) None reported c) None reported d) None reported	Human and Animals	**Design:** 30 Healthy humans and 40 mice were fed with IMO for 7 days and feces were determined before and at the end of the experiment for intestinal flora. **Results:** The production of Bifidobacteria and Lactobacillus greatly increased and the growth of Clostridium perfriengenes was significantly inhibited both in mice and in human intestinal tract. **Conclusions:** IMO could regulate and improve the intestinal flora in both mice and human intestine.	Gu et al. 2003

Type and Level of Evidence	Dosage: Dose, Dosage form, Frequency and route of administration	Duration, If any	Risk Information a) Caution or Warning b) Contraindication c) Adverse Reaction d) Other	Human: Animal; or *In vitro*	Design, Results and Conclusions	References
Experiment of rats	5% of basal diet	16 days, orally	a) None reported b) None reported c) None reported d) None reported	Animals	**Design**: The effect of isomaltulose, and other sugars were evaluated in respect of mineral absorption and retention. Wistar rats fed with non-digestible sugars and level of organic acids in cecum content were analyzed. **Results:** Organic acids in cecum content were increased by isomalt feeding, however, the pH values and acidity in cecum contents were not changed. **Conclusions:** Addition of non-digestible sugars like Isomaltulose, isomalt increased the cecum organic acids content resulting in increased uptake of minerals like Calcium, magnesium and phosphorous.	Kashimura et al 1996

*Randomized Control Trial

Type and Level of Evidence	Dosage: Dose, Dosage form, Frequency and route of administration	Duration, If any	Risk Information a) Caution or Warning b) Contraindication c) Adverse Reaction d) Other	Human: Animal; or *In vitro*	Design, Results and Conclusions	References
RCT* Level 1	30 g/d, orally	4 weeks	a) None reported b) None reported c) None reported d) None reported	Human	**Design:** Therapeutic efficacy of IMO in the treatment of chronic severe constipation and its effect on lipid profiles in 20 hemodialysis patients were evaluated. Bowel frequency, gastrointestinal effects, lipid profiles and biochemical paramenter were measured. **Results:** IMO induced a significant treatment. Some well-tolerated GI side-effects were noted. A significant decrease in total cholesterol and triglycerides and increased in HDL-C were noted. **Conclusions:** IMO once a day well tolerated, effective in increasing bowel frequency and improving constipation, lowering total cholesteroal and increase HDL-C.	Wang et al., 2001

Type and Level of Evidence	Dosage: Dose, Dosage form, Frequency and route of administration	Duration, If any	Risk Information a) Caution or Warning b) Contraindication c) Adverse Reaction d) Other	Human: Animal; or *In vitro*	Design, Results and Conclusions	References
RCT* Level 1	5-20 g/d, orally	12 days	a) None reported b) None reported c) None reported d) None reported	Human	**Design:** Effect of IMO was evaluated on human fecal bifidobacteria. 14 healthy adults men were fed 5, 10 and 20 g IMO/d with a 3-week interval for 12 days. Feces were evaluated for bifidobacteria. **Results:** IMO intake of 10g/d significantly increase the bifidobacterial numbers in feces and the ratio of fecal microflora with 12 days of treatment. **Conclusions:** IMO effectively increase the growth and number of bifidobacteria in humans.	**Kaneko et al., 1994**

Type and Level of Evidence	**Dosage: Dose, Dosage form, Frequency and route of administration**	**Duration, If any**	**Risk Information**) Caution or Warning) Contraindication) Adverse Reaction) Other	**Human: Animal; or *In vitro***	**Design, Results and Conclusions**	**References**
Experiment on rats	5%, 10% and 20% of daily diet, orally	6 weeks	a) None reported b) None reported c) None reported d) None reported	Animals	**Design:** To test the toxic effect of IMO in mammals, young rats were used and fed IMO-supplemented food for various %. The food intake and weight gain was measured twice a week, and at the end of six weeks, rats were sacrificed to examine the major organs for toxicity. **Results:** There was significant increase in weight of cecum, but no weight difference in other major organ of the body. **Conclusions:** IMO-supplemented food is non-toxic, and can reduce the formation or deposition of fat. It is predicted that, blood glucose level will be less in rats fed with IMO supplement.	**Donal et al., 2003**

Type and Level of Evidence	**Dosage: Dose, Dosage form, Frequency and route of administration**	**Duration, If any**	**Risk Information**) Caution or Warning) Contraindication) Adverse Reaction) Other	**Human: Animal; or *In vitro***	**Design, Results and Conclusions**	**References**
In vitro Experiment on rats	5-20 % diet, orally	5 weeks	a) None reported b) None reported c) None reported d) None reported	Animals	**Design:** Digestibility of the hydrogenated IMO was investigated. Rats were fed with 5-20% IMO diet supplement and body weight, organ's weight and food consumption was recorded every 2-3 days. **Results:** There was no gain in weight in any organ of the body except small intestine and cecum. No adverse effect like soft stool or diarrhoea observed. **Conclusions:** IMO partly digested by enzymes in the small intestine but less then that of maltose and maltooligosaccharides.	**Tsunehiro et al., 1999**

Overall Summary

There are numerous scientific studies that show that human consumption of IMO is generally safe. To our knowledge, there is no report yet published regarding any sever adverse reactions of IMO use in humans or in animals. Many Asian countries like Japan, China and Korea have already approved IMO as a functional health ingredient in various food items. According to Teruo (2003), the use of IMO is more prevalent in Japan than any other non-digestible oligosaccharide. In 2003, IMO demand in Japan was estimated at about 11,000 tons.

IMO is produced by the enzymatic transformation of starch and consists mainly of oligomers with two to four degree of polymerization, such as isomaltose, panose, and isomatotriose. Biological effects and safety of IMO on defecation frequency and blood lipid levels have been shown in young adults and experimental rodents (Liu 1994a, 1995b, Yang 1993). Administration of 10 g of IMO to healthy humans significantly improved defecation frequency and feelings of incomplete defecation (Liu 1994).

The effect and safety of IMO on Bowel-functions and nutritional status of elderly men was evaluated in detail (Chen 2001). The addition of 10g/d of IMO exerted significant effects on bowel function without any adverse influence on the nutritional status in constipated elderly humans. Although, daily stool output and stool weight per passage increased significantly with the supplement of IMO, but there was no indications of diarrhea. Also, the total number of intestinal microflora was observed to be increased significantly after IMO was consumed. Fecal total short-chain fatty acids (SCFA), acetate and propionate concentrations also significantly increased when IMO was consumed (Chen 2001). It has been reported that an increase in total amount of organic acids in feces represents the increased uptake of intestinal minerals like Calcium & Magnesium (Kashimura 1996). Hence, this represents the health benefit effects of IMO.

In Japan, IMO is used as prebiotic supplements and added to functional foods, while in Europe, IMO is used as milk replacers in animal feed or in pet food (Frost and Sullivan, 2003).

IMO has been used as a sweetener in Japan for many years. IMO syrup is effectively used for traditional fermented foods in Japan. The intake of these syrups not only improves the consistency of feces but also increase the microflora count in human intestine, thus effecting an improvement in colonic conditions as perbiotics without any adverse effect (Teruo 2003).

IMO is not a fermentable carbohydrate for oral bacteria. Also, it hardly forms any insoluble sucrose-containing polysaccharides on the surface of tooth that might support the bacterial growth resulting into dental cavities. Therefore, IMO could serve as a shield against tooth-decay from those foods that containing sucrose. This health benefit is particularly significant among infants and young children.

IMO is hardly metabolized by yeast and Lactobacillus. About 90% of total carbohydrate in IMO is low fermentable. Studies have showed that IMO is comparatively more resistance

toward intestinal digestion compared to Fructo-oligosaccharide (FOS). IMO is mildly sweet and have relatively low viscosity, high-moisture retaining properties and lower water activity compared to FOS, which lowers microbial growth and inhibit the synthesis of water insoluble glucan from sucrose.

In a separate clinical study, the effect of non-digestible oligosaccharides was evaluated on large-bowel functions, blood lipids concentrations and glucose absorption in young healthy male (Van Dokkum 1999). Results indicate that non-digestible oligosaccharies (like IMO) are partly fermented in the human colon, but in healthy young men the effects are limited. Also, the consumption of 15 g non-digestible oligosaccharides does not seem to alter blood lipid concentrations and glucose absorption in young adults (Van Dokkum 1999). Also, no adverse reaction or symptoms were reported during this randomized controlled trial.

Scientific data showed that, among the range of non-digestible sugar substitutes tested for maximum permissible dose at which transitory diarrhea is not caused, IMO has the safest with highest amount, i.e., >1.5 g/kg body wt (Oku 2002). The recommended maximum safe intake amount of IMO is 1.5-2.0 g/kg of body weight (b.w.) or about 15-20 g/day.

Based on the so far scientifically published data, knowledge and market information, there is reasonable certainty that the IMO is safe and does not pose any health related harm to general public under the intended conditions of use.

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List of Scientific References quoted

Following is the list of scientific publications that support the health benefits and consumption of IMO by human. References in bold are available in hard copy upon request;

1. Buecher B et al. Fructooligosaccharide associated with celecoxib reduces the number of aberrant crypt foci in the colon of rats. Reprod Nutr Dev 2003; 43(4):347-56.

2. **Chen HL, Lu YH, Lin JJ et al. Effects of Isomalto-oligosaccharides on bowel functions and indicators of nutritional status in constipated elderly men. J Am Col Nutr 2001; 20(1): 44-49.**

3. Chow J. Probiotics and prebiotics: A brief overview. J Ren Nutr 2002; 12(2):76-86.

4. **Donal A, Chang C-ho. 2003. A Dissertation submitted to Dept of Food Science, Louisiana State University, May 2002, by Chang-ho Chung. Patent Application Claims # 2004035789. page 15. Example 8 [Internet] Available from: http://www.freshpatents.com/Isomaltooligosaccharides-from-leuconostoc-as-neutraceuticals-dt20041125ptan20040235789.php?type=claims**

5. Frost and Sullivan. 2003, European Prebiotic Market. London, United Kingdom. Kashimura J, Kimura M, Itokawa Y. The effects of isomaltulose, isomalt and isomaltulose-based oligomers on mineral absorption and retention. Bio Trac Elem Res 1996; 54(3): 239-50.

6. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J Nutr 1995; 125(6):1401-12.

7. Gu Q, Yang Y, Jiang G et al. Study on the regulative effect of isomaltooligosaccharides on human intertinal flora. Wei Sheng Yan Jiu 2003; 32(1): 54-5.

8. Komoto T, Fukui F, Takaku H et al. Effect of isomalto-oligosaccharides on human fecal flora. Bifidobacteria Microflora 1988; 7:61-69.

9. Kashimura J, Kimura M, Itokawa Y., The effects of isomaltulose, isomalt and isomaltulose-based oligomers on mineral absorption and retention. Biol Trac Elem Res. 1996; 54 (3): 239-50.

10. Kashimura J, Kimura M, Itokawa Y. The effects of isomaltulose-based oligomers feeding and calcium deficiency on mineral retention in rats. J Nutr Sci Vitaminol (Tokyo) 1996; 42(1): 69-76.

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Submission End

GRN 000172

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12 July 2005

Susan J. Carlson, Ph. D.
Division of Biotechnology &
GRAS Notice Review, Office of the Food Additive Safety
Center for Food Safety & Applied Nutrition
Food & Drug Administration, USA

RECD JUL 25 2005

Ref: GRAS Notice No. GRN 00017 (dated July 7, 2005)

Dear Dr. Susan,

Thanks for your fax of dated July 7, 2005 regarding above mentioned GRAS Notice No. for our product IMO (Isomalto-oligosaccharide). We would like to make following amendments in our previously submitted GRAS letter (Notice No. GRN 00017) regarding the daily safe intake level of IMO as follows;

I) Recommended consumption level of IMO:

a) Recommended safe maximum IMO intake level when using as a Neutraceutical or natural health medicine (in forms of Pills or Capsules): **30 g/ day**

b) Recommended safe maximum IMO intake level when using as a general sweetener or food ingredient mixed with the other food ingredients: **2 g/kg of body weight**

(Oku T, Nakamura S. Digestion, absorption, fermentation and metabolism of functional sugar substitutes and their valuable energy. Pure Appl Chem 2002; 74(7): 1253-61).

II) In our previously submitted GRAS letter (Page 21, 2nd-last para, last line), we identified a typing error. It should be read as follows; **"The recommended maximum safe intake amount of IMO is 1.5-2.0 g/kg of body weight (b.w.)".**

Thanks very much and sorry for any inconvenience.

Best Regards,

(b)(6)

Jianhua Zhu, Ph. D.
(President/CEO)